REMARKS

Claims 1-38 are pending. Claims 6, 8-11, and 16-36 are withdrawn from consideration as directed to a non-elected species. Upon allowance of a generic claim, these claims should be examined in the present case. Claims 1-5, 7, 12-15, 37 and 38 are rejected. Claims 1-5, 7, 12-15, 37 and 38 remain in the case.

Claim 5 is rejected under the first paragraph of Section 112. According to the examiner, the LL2 antibody must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. Forwarded with this response are papers evidencing a deposit of the LL2 antibody that has been made in another of the assignee's cases. Withdrawal of the rejection of claim 5 is respectively requested.

Claims 1, 2, 4, 7 and 14 are rejected under Section 102(e) based on Aruffo *et al.* (U.S. 6,051,228). The examiner argues that

> Aruffo *et al.* teach a method of treating multiple sclerosis (MS) by administering a chimeric or humanized naked (*i.e.*, unconjugated) antibody to the CD40 antigen. Aruffo *et al.* teach that CD40 is a B cell determinant expressed on B cells (*e.g.*, column 1 at lines 14-22, and that antibody to CD40 depletes B cells when administered *in vivo* (*e.g.*, column 9 at lines 46 and column 12 at lines 37-55)

The portion of Aruffo *et al.* that is cited as teaching that CD40 is a B cell determinant expressed on B cells, does not in fact provide the alleged teaching. More particularly, Aruffo *et al.* teach in column 1, lines 14-22 that

> though ***originally*** identified as a B cell antigen, CD40 is ***now*** believed to be expressed by all antigen presenting cells (APC), including dendritic cells, keratinocytes, and monocytes. CD40 is also express by cell types that can act as APC under certain conditions, such as vascular endothelial cells, or cells involved in direct interactions with T cells or T cell precursors such as thymic epithelial cells. More recently, it has also been reported that CD40 can be expressed by fibroblasts, eosinophils, and activated T cells. CD40 expression has also been seen in cancerous cells.

Thus, a key premise on which novelty is asserted is missing from the reference. In order to emphasize this distinction further, claim 1 has been amended to recite that the B-cell antigen is selected from the group consisting of CD22, CD20 and CD19. These B-antigens are specific to B-cells, while CD40 is expressed on many other cell types in addition to B-cells. These include basal epithelial cells plus epithelial cell carcinomas, macrophages, follicular dendritic cells, endothelial cells, fibroblasts, keratinocytes, interdigitating cells, and CD34+ hemopoietic cell progenitors. No possible anticipation of claims 1, 2, 4, 7 and 14 as amended exists based on Aruffo *et al.*

Claims 1-4, 7, 12-15, 37 and 38 are rejected under Section 103(a) based on the combined teachings of Aruffo *et al.*, Meyer *et al.*, Anderson *et al.*, Tedder *et al.*, and The Merck Manual of Diagnosis and Therapy. Claim 5 is rejected on the same references taken in view of Leung *et al.*

The examiner's characterization of Aruffo *et al.* already has been discussed. Meyer *et al.* is cited as teaching "that the B cell response in mammals can be suppressed by administering antibodies," either unconjugated (*i.e.*, "naked", see page 3 at line 31) or conjugated, to surface antigens of the B cell (see entire document, *e.g.*, Abstract and claims). Anderson *et al.* is cited as teaching the production of a chimeric anti-CD20 antibody and the use of this antibody to deplete nonmalignant B cells *in vivo*. Tedder *et al.* is relied upon as teaching antibodies to the B cell surface protein CD22 and their use in blocking B cell function, and their use in treating autoimmune disease.

The basis for substituting and/or combining features from one or more of the secondary references is that ***CD40 is a B cell antigen***. Thus, for example, the examiner states that "Meyer *et al.* teach that in order to effectively regulate B cell responses *in vivo*, antibodies to ***multiple B cell surface antigens*** should be combined. Anderson *et al.* and Tedder *et al.* teach naked (*i.e.*, unconjugated) antibodies to CD20 and CD22 that can each be used to regulate ***B cell responses in vivo***." As explained above, Aruffo *et al.* teaches that CD40's characterization as a "B cell antigen" has been superceded by more recent recognition of its presence on a variety of cell types. Attached to the present response is a

copy of a web page http://www.biocarta.com/pathfiles/h_asbcellPathway.asp, which explains the relationship between B cell antigens and CD40. As noted, "The body produces B cells with a wide range of antigen specificities in the immunoglobulin B cell receptor, ***one antigen specificity per cell***.... CD40 interaction with CD40L and CD28 interaction with CD80 provide positive costimulatory signals that stimulate B cell activation and proliferation. T cell receptor activation induces expression of molecules like the CD40 ligand that modulate the B cell-T cell interaction. The CD40-CD40L interaction induces cytokine production and expression of other genes and alters the fate of the B cell involved in the interaction." Clearly, CD40 is not a B cell antigen like CD22, CD20 and CD19, each of which is specific to one B cell type. Accordingly, it would not have been obvious to substitute an antibody to one of the B cell antigens disclosed in Anderson *et al.*, Meyer *et al.* or Tedder *et al.* for an antibody to the CD40 antigen in Aruffo *et al.*

Furthermore, the only two documents that purport to teach treatment of an autoimmune disease with a B cell antibody are Aruffo *et al.* and Tedder *et al.* However, the mechanism proposed by Aruffo *et al.* is not related to the presence of CD40 on B cells, but rather on a blocking of the interaction between gp39 and CD40, which blocks humoral immune responses to T cell dependent antigens. Accordingly, Aruffo *et al.* cannot possibly suggest treatment of autoimmune disorders with at least one antibody to a B-cell antigen selected from the group consisting of CD22, CD20 and CD19. Aruffo *et al.* does not suggest a mechanism that involves antibodies to B cell antigens, and thus provides no teaching relevant to the treatment of autoimmune disorders using B cell antibodies as presently claimed. Aruffo *et al.* is clearly deficient as a teaching under Section 103(a).

The only other document that suggests the treatment of autoimmune disorders with an antibody to a B cell antigen is Tedder *et al.*, which is based on an entirely different mechanism. Tedder discloses "a series of novel monoclonal antibodies (mAb), designated HB22, that specifically block cell adhesion to CD22, an adhesion receptor expressed by mature lymphocytes" (column 4, lines 32-35). These antibodies identify a region of the CD22 receptor that is distinct from those defined by previously described CD22

monoclonal antibodies, and act by blocking CD22 adhesive function. The adhesion mechanism in Tedder *et al.* is entirely different from the mechanism proposed by Aruffo *et al.* which is related to a blocking of the interaction between gp39 and CD40 to block humoral immune responses to T cell dependent antigens. Thus there would have been no motivation to substitute one of Tedder's antibodies for the CD40 antibody of Aruffo *et al.*, or to combine Tedder *et al.* with Aruffo *et al.*

The Merck Manual is cited as disclosing that the cytokine IFN-β is a standard therapy for MS. It does not overcome the failure of Aruffo *et al.*, Meyer *et al.*, and Tedder *et al.* to teach a method for treating an autoimmune disorder, comprising administering to a subject having an autoimmune disorder a therapeutic composition comprising a pharmaceutically acceptable carrier and at least one antibody to a B-cell antigen selected from the group consisting of CD22, CD20 and CD19.

In view of the foregoing remarks, all claims are believed to be in condition for allowance. Should the examiner require anything further, she is invited to contact the undersigned at the local exchange provided below.

Respectfully submitted,

Date February 5, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method for treating an autoimmune disorder, comprising administering to a subject having an autoimmune disorder a therapeutic composition comprising a pharmaceutically acceptable carrier and at least one antibody to a B-cell antigen selected from the group consisting of CD22, CD20 and CD19.

12. (Amended) The method of claim 1, wherein said B-cell antigen is [selected from the group consisting of CD19,] CD20[, CD22, HLA-DR and CD74].

PATHWAYS ▸ Antigen Dependent B Cell Activation

▸ REVISION HISTORY

Submitted by: **Gregg Hickey, PhD** ▸ Guru: ▸

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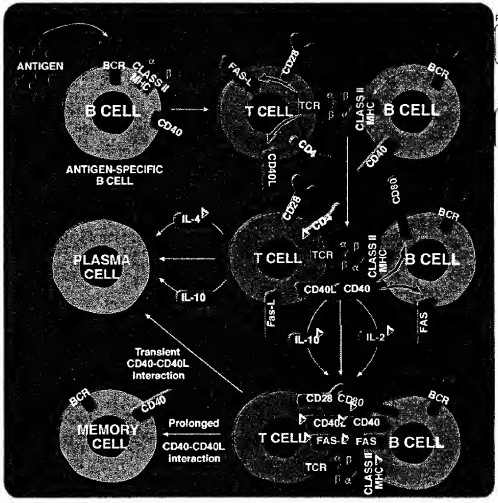

May 2000

This Pathway
Other Species:

DESCRIPTION: A key part of the immune system is the production of immunoglobulins (antibodies) by B cells to bind and inactivate specific foreign antigens. The body produces B cells with a wide range of antigen specificities in the immunoglobulin B cell receptor, one antigen specificity per cell. When the B cell receptor immunoglobulin binds antigen, that cell is activated to proliferate and create plasma cells secreting immunoglobulins to bind that specific antigen. B cell activation also creates memory cells with the same antigen specificity that do not actively secrete immunoglobulin but provide for rapid future immune responses to the same antigen.
B cells are not activated by antigen on their own, but require interaction with helper CD4+ T cells to become activated and proliferate. The B cell first expresses immunoglobulin on the cell surface as the B cell receptor. If the B cell receptor immunoglobulin binds specific antigen, then the cell internalizes the antigen and presents it to T cells in MHC II, where it is recognized by the T cell receptor. In addition to the interaction between the T cell receptor and the B cell MHC-antigen, T cell interaction with the B cell involves additional positive and negative regulatory signals. CD40 interaction with CD40L and CD28 interaction with CD80 provide positive costimulatory signals that stimulate B cell activation and proliferation. T cell receptor activation induces expression of molecules like the CD40 ligand that modulate the B cell-T cell interaction. The CD40-CD40L interaction induces cytokine production and expression of other genes and alters the fate of the B cell involved in the interaction. If the interaction between CD40 and CD40L is prolonged, the B cell can be induced to become a memory cell rather than a plasma cell. Fas ligand binding to Fas between B and T cells may negatively modulate B cell activation, inducing apoptosis that limits B cell proliferation and activation. Cytokines like IL-2, IL-4 and IL-10 also play an important role in B cell activation.

CONTRIBUTORS: Glenn Croston, PhD.

REVISION HISTORY:

REFERENCES: